RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 1-11 were pending prior to the Office Action dated November 20, 2002. For the Examiner's convenience, the pending claims are attached hereto as Appendix A.

B. Claims 1-4 and 6-11 Are Definite

The Action rejects claims 1-4 and 6-11 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as the invention. It contends that the specification defines "infectious nucleic acid" as full-length cDNAs or RNA transcripts that are infectious in cell culture. The Action further argues that the term "isolated and purified" is defined as a nucleic acid molecule that is not part of an intact GVB-C virus. It concludes that the claim is not clear because it can be interpreted in two ways: (1) to require full-length cDNA and RNA transcript that is different than those described because it is able to replicate *in vitro*; or (2) to involve less than a full-length clone, requiring anywhere from 10-12000 nucleotides. Applicants traverse this rejection.

The Action is incorrect about the specification's definition of "infectious nucleic acid." On page 6, the specification, the subheading "Infectious Nucleic Acids" is under the general heading of "Description of Related Art" and the text accompanying the subheading describes the art and its teaching of infectious nucleic acids—the text does not describe the present invention. The text states: "Full length cDNA or RNA transcripts of several RNA viruses including hepatitis A virus, GBV-B, and HCV are infectious in cell culture or animal inoculation studies. . . ." (citations omitted). Notably, GVB-C is absent from that description. It is inappropriate to use a characterization of what the prior art has taught to define the present invention. Furthermore, simply because the subheading is "Infectious Nucleic Acids" does not mean that a description of what the prior art has taught is a complete definition of that

subheading, as opposed to examples of what qualifies as an infectious nucleic acid. There is no reason that a person of ordinary skill in the art would believe that infectious nucleic acids are *limited* to full-length cDNAs or RNA transcripts; instead, that person reading the specification would understand that some examples of infectious nucleic acids of viruses other than GVB-C virus have been full-length.

The specification makes clear that the term "infectious nucleic acids" is not limited to full-length sequences. Under the section "Summary of the Invention," the specification states:

> The compositions and methods of the present invention take advantage of the discovery of an isolated and purified nucleic acid molecule encoding an infectious GVB-C. . . . These nucleic acid molecules have been produced in the form of a DNA construct or expression construct, as well as an infectious full-length GBV-C RNA transcript expressed from the DNA construct (collectively referred to as "recombinant GBV-C"). A cDNA clone made from the full-length or a less-than full-length transcript is also contemplated within the scope of the invention.

Specification at pp. 6-7. Thus, full-length and less-than full-length transcripts are understood as part of the invention.

The claims are directed to an "isolated and purified nucleic acid molecule encoding an infectious GBV-C." The standard for definiteness of a claim is whether a person of skill in the art can determine the scope of the invention based on the language of the claims with "a reasonable degree of certainty." MPEP 2173.02 (citing *In re Wiggins*, 488 F.2d 538, 179 U.S.P.Q. 421 (C.C.P.A. 1973)). The specification indicates that the phrase "isolated and purified" refers to a "nucleic acid molecule [that] is not part of an intact GVB-C virus." Specification at page 6. Furthermore, the specification also makes it clear that a nucleic acid molecule encoding an infectious GVB-C refers to a nucleic acid that is infectious and contains GVB-C sequence. Specification at page 7. Therefore, based on the specification, a person of skill in the art can determine the scope of the invention with "reasonable certainty." Applicants respectfully request this rejection be withdrawn.

C. Claims 1-4 and 6-11 Are Enabled

The Action rejects claims 1-4 and 6-11 under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not reasonably provide enablement for an infectious nucleic acid that is less than or greater than the full-length clone. While the Action admits the specification is enabled for an infectious full-length clone of GBV-C that corresponds to SEQ ID NO:1, it argues that a single example utilizing a full-length clone does not provide sufficient guidance to make infectious clones that may be smaller or larger in size. The Action cites Pang *et al.* ("Pang") as supporting its position that the art is unpredictable because this article purportedly shows that structural proteins can be replaced with heterologous sequences, but that the resulting nucleic acids are not infectious and do not produce particles. It concludes that one of ordinary skill in the art would not be able to reproducibly practice the entire scope of the invention as claimed, without undue experimentation. Applicants traverse this rejection.

In examining a patent application, the PTO is required to assume that the specification complies with the enablement provisions of Section 112 unless it has "acceptable evidence or reasoning" to suggest otherwise. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-370 (CCPA. 1971). The PTO thus must provide reasons supported by the record as a whole what the specification is not enabling. *Application of Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219-220 (CCPA 1979). Then and only then does the burden shift to the applicant to show that one of ordinary skill in the art could have practiced the claimed invention without undue experimentation. *In re Strahilevitz*, 668 F.2d. 1229, 1232, 212 USPQ 561, 563-64 (CCPA 1982).

In the present case, the Action cites the Pang reference because it purportedly shows an attempt to produce infectious virus from a replicon RNA that contained heterologous sequences in place of endogenous viral genes. However, this reference does not shift the burden to the applicant because the Pang reference has nothing to do with hepatitis viruses, much less GVB-C.

The Pang reference is entitled "Development of dengue virus replicons expressing HIV-1 gp120 and other heterologous genes: potential future tool for dual vaccination against dengue virus and HIV." The Pang reference describes engineered nucleic acid molecules from the dengue virus, which is not a hepatitis virus.

Furthermore, the Pang reference makes it clear that the authors are attempting to engineer a vaccine against dengue virus, in which case they do not want an infectious nucleic acid. This is supported by their Conclusion in which they state: "Although our successful development of a plasmid which can express a dengue replicon from transfected DNA facilitates delivery by DNA vaccination, the development of packaging cell lines which can package these replicons into virions would be a major step forward towards a vaccine . . . ." Pang at p. 6. Because the Pang reference indicates the authors were trying to avoid obtaining an infectious nucleic acid, which they successfully achieved, this does not show that there is unpredictability in the art about what size of heterologous sequence can be inserted into the GVB clone while maintaining infectiousness.

Applicants respectfully note that "it is incumbent upon the Patent Office...to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." MPEP 2164.04 (quoting *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (CCPA 1971)). In citing the Pang reference, the Office has not done this because it is not sufficient to cite to a reference that did not accomplish a particular goal of the invention—*i.e.,* infectious nucleic acids with substitutions—when the paper makes it clear that it wanted to avoid such a goal.

Moreover, the test of enablement is whether the experimentation needed to practice the invention is undue. MPEP § 2164.01 (citing *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916)). The instant specification shows how to construct an infectious GVB-C nucleic acid (Examples 1 and 2), as well as how to analyze it and assay it for infectivity (Examples 3 and 4). The generation of deletions, substitutions, insertions and other additions is well known to those of ordinary skill in the art through the use of recombinant nucleic acid technology. On pages 18-36, basic information regarding the manipulation of nucleic acids is provided. There is no reason a person of ordinary skill in the art could not use the teachings of the specification to generate additional infectious GVB-C nucleic acids. Satisfaction of the enablement requirement is not precluded by the necessity of some experimentation. *See Atlas Powder Co. v. E.I. duPont De Nemours & Co.,* 750 F.2d 1569, 1576, 224 U.S.P.Q. 409 (Fed. Cir. 1984). There is no evidence such experimentation would be undue.

Accordingly, Applicants respectfully request this rejection be withdrawn.

D. The Claims Are Not Anticipated by the Prior Art

1. Claims 1-4, 6-7, and 9-10 Are Not Anticipated by Kim *et al.*

The Action rejects claims 1-4, 6-7, and 9-10 under 35 U.S.C. § 102(b) as being anticipated by Kim *et al.* (U.S. Patent No 5,856,134) ("Kim"). It contends that Kim discloses the entire coding region of two hepatitis-G virus DNA clones and that it further discloses the "expression and purification of HGV virus protein [sic]." (Applicants have assumed the Action meant an HGV virus "particle.") The Action interpreted the claims of the instant invention to encompass sequences that are less than full-length GVB-C, and consequently, determined the claims were anticipated by Kim. Applicants respectfully traverse this rejection.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987).

The claims recite an "isolated and purified nucleic acid molecule encoding an infectious GBV-C." Even if the claims are construed to cover less than full-length nucleic acid molecules, an express limitation of the claim is that the nucleic acid molecule encode an *infectious* GVB-C. Prior to the present application, no one had shown such a molecule existed. Applicants were the first to invent an infectious nucleic acid that was isolated away from GVB-C viral particles. Kim does not teach any such nucleic acid molecule, nor does the Action identify any disclosure of such a molecule in Kim. Without a disclosure of an *infectious* GVB-C virus or clone, the Kim reference does not teach an element of the claimed invention.

The Examples disclosed in Kim do not show that an *infectious* GVB-C molecule was obtained. As discussed in the Declaration of Jack Stapleton ("Declaration"), the Kim reference shows in Examples 5 and 6 the isolation of HGV viral particles and then the isolation of clones corresponding to segments of the HGV genome. As described in Example 6, the authors then juxtaposed the sequences together to configure SEQ ID NOs:14 and 182. However, the claims require an *infectious* GVB-C nucleic acid. As the Declaration makes clear, the Kim reference never discloses that the sequences were joined in an intact nucleic acid molecule. As such, the Kim reference does not show its authors had an "isolated and purified nucleic acid molecule encoding an infectious GBV-C." Moreover, the reference does not indicate that any of the segment clones, singly or when joined with other segment clones, were infectious in culture.

Furthermore, there is no reason to believe SEQ ID NOs:14 and 182 are infectious. The Declaration notes, "the serum from which the clones were made was never shown to have been tested for infectivity."

Accordingly, the Kim reference does not teach each and every element of the claimed invention. Therefore, Kim does not anticipate claims 1-4, 6-7, and 9-10. Applicants respectfully request this rejection be withdrawn.

2. Claims 1 and 2 Are Not Anticipated by Xiang *et al.*

The Action rejects claims 1 and 2 under 35 U.S.C. § 102(b) as being anticipated by Xiang *et al.* ("Xiang"). Xiang is said to disclose RNA extraction (isolation and purification) of HGV RNA from patient plasma samples. The Action concludes that Xiang anticipates the claimed invention to the extend the claims are interpreted to as sequences that can be less than full-length GVB-C. Applicants respectfully traverse this rejection.

Again, in order for a reference to anticipate a claim, each element of the claim must be disclosed or taught in the cited reference. The Xiang reference does not teach an "infectious" nucleic acid molecule. It does not mention any assays being conducted to determine whether the isolated molecules were infectious. In fact, according to the Declaration, the infectivity of isolated GVB-C RNA molecules was never tested.

Accordingly, Xiang fails to teach an element of the claimed invention. Therefore, it does not anticipate claims 1 and 2. Applicants respectfully request this rejection be withdrawn.

3. Claims 1-3, 6, and 9-11 Are Not Anticipated by Pilot-Matias *et al.*

The Action rejects claims 1-3, 6, and 9-11 under 35 U.S.C. § 102(e) as being anticipated by Pilot-Matias *et al.* (U.S. Patent No. 6,156,495) ("Pilot-Matias"). It contends that Pilot-Matias discloses the production of fusion proteins comprising HGBV virus sequences, the nucleic acids encoding the HGBV virus sequences are inserted into a pSFV1 construct, which contains the

heterologous promoter Sp6. As such, the Action contends that the instant claims are anticipated by Pilot-Matias *et al.* Applicants respectfully traverse this rejection.

As disclosed in the specification of the present application, what was invented by the inventors was a GVB-C nucleic acid that is infectious and not included in a viral particle. The cited references, including the Pilot-Matias reference, fail to anticipate the claimed invention because the inventors of the present application were the first to disclose an isolated and infectious GVB-C nucleic acid. The Declaration states that the Pilot-Matias reference "does not show the infectivity of any nucleic acids from a GVB-C, nor does it show that the serum from which GVB-C particles was isolated contains infectious virus."

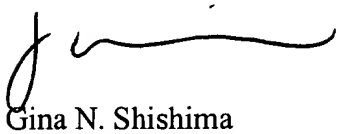
Patent law requires identity between the reference and the claimed invention. Having fallen short, the Pilot-Matias reference cannot anticipate the claimed invention. Applicants respectfully request this rejection be withdrawn.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so they may pass to issuance.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner, the Examiner's supervisor, and the undersigned attorney at 512-536-3081 is respectfully requested.

Respectfully submitted,



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